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PRINCIPAL INVESTIGATOR: Mark L. Laudenslager, Ph.D.

CONTRACTING ORGANIZATION: University of Colorado Health Sciences Center
Aurora, Colorado 80045-0508

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Mark L. Laudenslager, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Colorado Health Sciences Center
Aurora, Colorado 80045-0508

E-Mail: Mark.Laudenslager@uchsc.edu

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Preeclampsia has been linked to reduced breast cancer risk, and this reduction may be especially marked among women who bear their first child later in life. In this ongoing case-control study, we examine the hormonal profiles of older Colorado mothers with and without a history of preeclampsia in their first pregnancies. Subjects are nonpregnant, non-smoking women who completed their first pregnancies at age 30 or older, are currently premenopausal, and are free of serious chronic disease. Cases are 14 Denver area women who experienced preeclampsia in their first pregnancy; controls are 13 women with uncomplicated first pregnancies, frequency matched to cases on race/ethnicity, current age, age at delivery, and breast-feeding status. A fasting blood and saliva sample was collected from each subject during the luteal phase (day 19-22) of the menstrual cycle and assayed for specific steroid and peptide hormones thought to be linked to breast cancer.

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PREECLAMPSIA-ASSOCIATED HORMONAL PROFILES AMONG OLDER MOTHERS

Department of Defense Breast Cancer Concept Award: BC996307 (DAMD17-00-1-0617)
Final Report

ABSTRACT

Preeclampsia has been linked to reduced breast cancer risk, and this reduction may be especially marked among women who bear their first child later in life. In this ongoing case-control study, we examine the hormonal profiles of older Colorado mothers with and without a history of preeclampsia in their first pregnancies. Subjects are nonpregnant, non-smoking women who completed their first pregnancies at age 30 or older, are currently premenopausal, and are free of serious chronic disease. Cases are 14 Denver area women who experienced preeclampsia in their first pregnancy; controls are 13 women with uncomplicated first pregnancies, frequency matched to cases on race/ethnicity, current age, age at delivery, and breast-feeding status. A fasting blood and saliva sample was collected from each subject during the luteal phase (day 19-22) of the menstrual cycle and assayed for specific steroid and peptide hormones thought to be linked to breast cancer.

INTRODUCTION

Recent research indicates that preeclampsia is associated with reduced breast cancer risk1, and that this risk reduction is greatest among women who bear their first child later in life[2]. This protective effect is likely due to a unique underlying hormonal profile that both predisposes to preeclampsia and reduces breast cancer risk[1]. For example, previous studies suggest that insulin resistance may be linked both to the development of preeclampsia, and to lower breast cancer risk[1]. Similarly, insulin-like growth factor, shown to be reduced in preeclamptic women, is a potent mitogen and antiapoptotic agent thought to play an important synergistic role with estrogens in the pathogenesis of breast cancer[1]. However hormonal studies of nonpregnant women with a history of preeclampsia are limited, and none have yet examined the hormonal profiles of women who experienced preeclampsia as older first-time mothers.

BODY

This ongoing case-control study examines hormonal profiles of older mothers with and without a history of preeclampsia in their first pregnancies. Subjects are normoglycemic, normotensive nonpregnant, women who completed their first pregnancies at age 30 or older, are currently premenopausal, do not smoke, are free of serious chronic disease, and do not have a personal history of cancer. Cases are women who experienced preeclampsia in their first pregnancy; controls are women with uncomplicated first pregnancies and no history of preeclampsia, frequency matched to cases on race/ethnicity, current age, age at delivery, and breast-feeding status. Women were recruited from the local Denver, CO community. A fasting blood and saliva sample was collected from each subject during the luteal phase (day 19-22) of the menstrual cycle and assayed for specific steroid and peptide hormones thought to be linked to breast cancer. We gathered data on 27 women, 14 with and 13 without a history of preeclampsia.

Analysis: Differences between cases and controls were initially assessed using chi square (for categorical variables), student unpaired t tests (for continuous variables with a normal distribution), or Mann-Whitney U tests (for continuous or ordinal variables with evidence of skewing). We used logistic regression to evaluate the independent associations of specific hormone levels to a woman's history of preeclampsia. The IGFBP-3/IGF-1 ratio was calculated using the molecular weights of these compounds. To measure insulin resistance, we used the Fasting Insulin Resistance Index (FIRI), calculated as fasting glucose*fasting insulin/25 [3-5].

KEY RESEARCH ACCOMPLISHMENTS & REPORTABLE OUTCOMES

Relative to women with uncomplicated pregnancies, those with a history of preeclampsia in their first pregnancies completed their first pregnancies more recently, were more likely to be primiparous at the time of the study, and had higher resting diastolic and systolic blood pressures (Table 1). There were no differences in current age, age at first delivery, racial/ethnic distribution, history of breast feeding, history of smoking or family history of breast cancer. Although cases averaged higher BMI's than did controls, the difference was not significant.

Table 1. CHARACTERISTICS OF WOMEN WITH AND WITHOUT PRIOR PREECLAMPSIA (N (%) OR MEAN (SE))

	History of Preeclampsia		
	Yes (n=14)	**No (n=12)**	**p value**
Current age (y)	37.1 (1.2)	38.2 (1.4)	0.53
Non-Hispanic White	10 (71.4%)	10 (76.9%)	0.75
Age at delivery (y)	34.2 (0.9)	33.4 (1.0)	0.56
Years since delivery	2.9 (0.6)	5.25 (0.7)	**0.01**
Primiparous	11 (78.6%)	5 (38.5%)	**0.03**
Number live births	1.2 (0.1)	1.8 (0.2)	**0.05†**
Number of pregnancies	2.0 (0.29)	2.9 (0.57)	0.10†
Age at menarche (y)	12.3 (0.3)	13.0 (0.3)	0.07
Current BMI	27.5 (1.7)	23.6 (0.9)	0.12†
Breastfed infant	12 (85.7%)	12 (92.3%)	0.59
Time breast fed (months)	8.0 (1.8)	11.1 (2.4)	0.32
Ever smoked	5 (35.7%)	5 (41.7%)	0.88
Midcycle diastolic BP	70.7 (2.4)	59.1 (3.9)	**0.02†**
Midcycle systolic BP	113.8 (3.7)	104.8 (3.3)	**0.04**

NOTE: Cases with extreme obesity (BMI>42) excluded

†p-value calculated using Mann-Whitney U rank sum test; all others calculated using unpaired t-test

Compared to women with uncomplicated pregnancies, those with a history of preeclampsia had significantly elevated levels of serum triglycerides, insulin and glucose, and a higher fasting insulin resistance index (Table 2 and Fig 1), suggesting that women with prior preeclampsia were relatively insulin resistant.

Table 2. MID-CYCLE HORMONE AND LIPID LEVELS

	History of Preeclampsia		
	Yes Mean (SE)	**No Mean (SE)**	**p value**
Lipids			
Cholesterol (mg/dl)	198.0 (12.9)	195.3 (8.0)	0.85
HDL-Total (mg/dl)	52.8 (5.2)	59.3 (2.0)	0.27
Triglycerides (mg/dl)	175.5 (39.2)	76.8 (9.3)	**0.005**
Steroid Hormones			
DHEA (ug/dl)	113.3 (27.1)	108.5 (11.8)	0.78
Estradiol (pg/ml)	109.8 (9.7)	94.7 (9.7)	0.28
Progesterone (ng/ml)	9.8 (1.8)	10.9 (2.7)	0.71
Salivary TestosteroneST10	67.0 (15.2)	88.5 (12.9)	0.31
Peptide Hormones			
SHBG (nM/L)	104.9 (20.8)	115.6 (13.4)	0.23
IGF-1 (ng/ml)	159.6 (9.5)	183.7 (115.1)	0.18
IGFBP-3 (ng/ml)	3414.1 (163.1)	2858.2 (168.9)	**0.03**
IGFBP-3/IGF-1 (molar ratio)	118.5 (6.6)	90.5 (7.47)	**0.01**
Insulin (uU/ml)	13.1 (2.2)	7.0 (0.6)	**0.008**
Glucose (mg/dl)	90.0 (3.8)	80.9 (1.2)	**0.05**
Fasting Insulin resistance index	2.7 (0.8)	1.3 (0.1)	**0.03†**

In addition, cases had lower levels of serum insulin-like growth factor (IGF-1) after adjustment for obesity and other potential confounders (OR=0.7 per 10 ng/ml, 95% CI 0.5-1.0), and demonstrated higher levels of IGF binding protein 3 and a higher ratio of IGF binding protein-3 (IGFBP-3) to IGF-1 than did controls (Table 2 and Fig 2). Adjustment for parity, and years since the index pregnancy reduced the association of IGFBP-3 to history of preeclampsia, but did not appreciably alter that of other factors (Fig. 3). Similarly, excluding multiparous women (N=11), those who had given birth to their first child more than five years before (N=6), or those on prescription medications (N=6) did not substantively alter the observed relationships, nor did additional adjustment for obesity. Cases and controls did not differ significantly in serum or salivary steroid levels (estradiol, progesterone, DHEA, or testosterone) or in serum cholesterol or HDL levels.

CONCLUSIONS AND IMPLICATIONS

Relative to older mothers with uncomplicated pregnancies, those with a history of preeclampsia in their first pregnancy had increased levels of triglycerides, insulin, and glucose, an increased fasting insulin resistance index, reduced levels of IGF-1, increased IGFBP-3 levels, and an elevated ratio of IGFBP-3 to IGF-1. These preliminary findings, while based on small sample sizes, suggest that certain physiological alterations characterizing pregnant women who develop preeclampsia, i.e., reduced bioavailability of IGF-1 and increased insulin resistance, may persist post-pregnancy and may underlie the observed reduction in risk for breast cancer observed among older primiparas with a history of preeclampsia. This conclusion must be validated in women with a BMI of less than 30. These very promising results await confirmation in a larger study.

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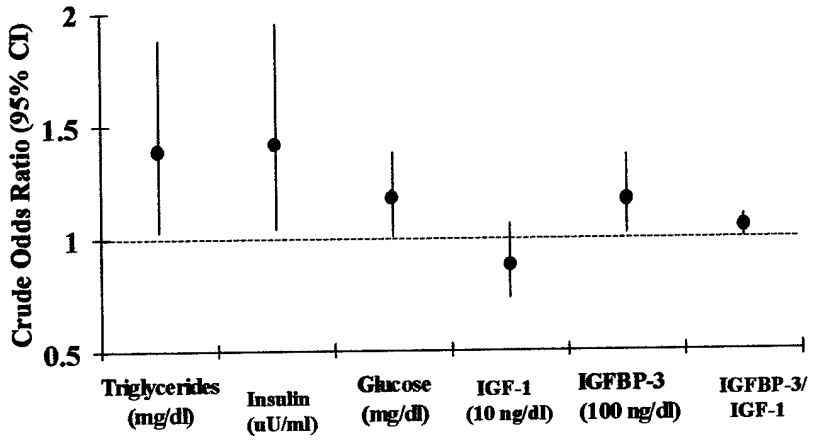
PERSONNEL

Kim (Karen) E. Innes, MSPH, PhD (Co-Principal Investigator)
Mark L. Laudenslager, PhD (Acting Principal Investigator
Ashley Ross May (Research Assistant)
Lindsay B. Weitzel, MS (Research Assistant)

Figure 1. Association of lipid, hormone, and glucose levels with a history of preeclampsia



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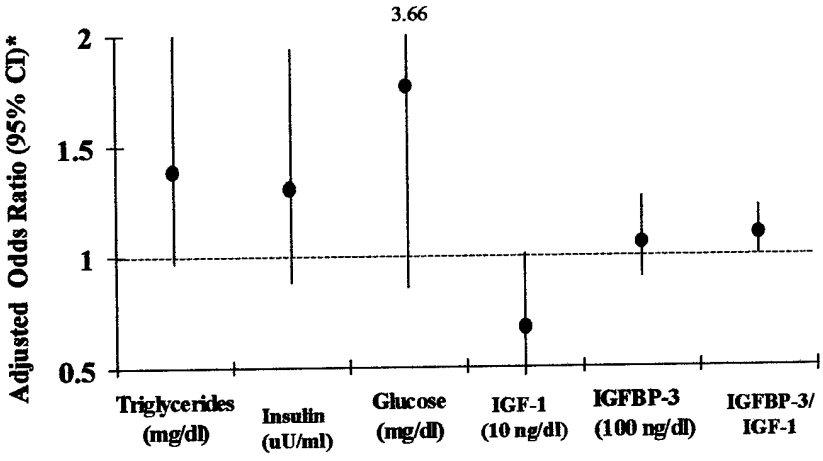
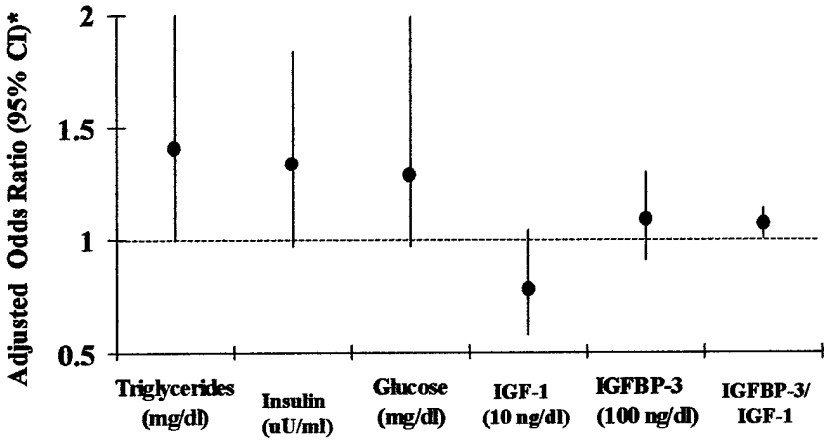


*Adjusted for parity, years since index pregnancy, and obesity

Figure 3. Association of lipid, hormone, and glucose levels with a history of preeclampsia



*Adjusted for parity and years since index pregnancy